CASE REPORTS

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Disseminated Strongyloidiasis

A Complication of the Immunosuppressed Host

TIMOTHY T. KUBERSKI, MD
E. PETER GABOR, MD
DAVID BOUDREAUX, MD
Los Angeles

INFECTION WITH Strongyloides stercoralis, a nematode intestinal parasite, usually is asymptomatic or produces only mild gastrointestinal symptoms in healthy persons. However, the infection can become fulminant and lethal when immunosuppression has been produced through natural or iatrogenic means.[1-12]

The present case of fatal strongyloidiasis developed in a young woman receiving chemotherapy for acute lymphoblastic leukemia. The patient had lived continuously in Los Angeles after immigrating from Costa Rica in 1956. The case is presented to emphasize the occult nature of Strongyloides infection in the United States and to point out the importance of diagnosing and treating this infection before beginning immunosuppressive therapy.

Report of a Case

A 31-year-old Costa Rican woman presented with complaints of fatigue, weakness and dizziness. Results of hematologic evaluation showed severe anemia, lymphocytosis and thrombocytopenia. A bone marrow aspirate was diagnostic of acute lymphoblastic leukemia.

From the Departments of Medicine and Pathology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, CA 90024.

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Reprint requests to: T. T. Kuberski, MD, Pacific Research Section, National Institute of Allergy and Infectious Diseases, P.O. Box 1680, Honolulu, HI 96806.

On admission to the University of California, Los Angeles, Medical Center on 16 March 1973, the patient said there had been no history of bleeding problems and had no gastrointestinal complaints. Except for obesity, findings on physical examination were unremarkable.

Laboratory data included: hemoglobin 10.7 grams; hematocrit 31.4 percent; leukocyte count 5,500 per cu mm with 61 percent undifferentiated cells. The platelet count was 66,000 per cu mm. Findings on kidney and liver function tests were within normal limits. Results of an intermediate-strength purified protein derivative of tuberculin and coccidioidin skin tests were negative; results of a skin test for mumps were positive. On a bone marrow aspirate, sheets of immature cells resembling lymphoblasts, very few normoblasts and myeloblasts and rare megakaryocytes were noted. Examination of three stool specimens showed no ova and parasites. One of 23 differential leukocyte counts showed a 13 percent eosinophilia with the remainder between 0 and 1 percent eosinophils.

Therapy with vincristine sulfate and prednisone resulted in a remission; after four weeks the peripheral blood count was normal and a bone marrow aspirate showed a hypocellular marrow with 5 to 10 percent degenerating blast cells. The patient was discharged on a maintenance regimen consisting of prednisone and 6-mercaptopurine, as well as isoniazid. The 6-mercaptopurine was eventually discontinued because of the development of leukopenia.

Two subsequent admissions to hospital were necessitated by high fever, chills, anemia, thrombocytopenia and the development of ulcerative perineal lesions. While the patient was in the hospital, no gastrointestinal or pulmonary abnormalities were observed. Numerous cultures of the blood, sputum, urine, stool, cerebrospinal fluid, throat and perineal lesions were negative for pathogenic organisms. No chemical abnormalities or pleocytosis were observed in the cerebrospinal fluid. The patient responded to corticosteroids, antibiotics and transfusion therapy with clinical defervescence and symptomatic improvement. The cutaneous perineal ulcers partially healed and on

discharge hemoglobin was 11.6 grams; hematocrit 33.6 percent; platelet count 120,000 and leukocyte count 6,000 per cu mm, with a differential of 46 percent segmented neutrophils, 3 percent bands, 46 percent lymphocytes and 3 percent eosinophils. Several bone marrow aspirates showed normal megakaryocytes, active erythropoiesis and granulopoiesis with no leukemic cells.

The patient remained well on no maintenance therapy until admission for the fourth time on 23 July 1973 following five days of nausea, vomiting and weakness, and an episode of hematemesis. According to the patient, there had been no abdominal pain, diarrhea, melena, fever or chills. On physical examination, the patient was seen to be obese, Cushingoid, alopecic, lethargic and pallid, with extensive purpura over the arms, chest and abdomen. Pulse was 140 beats per minute; blood pressure 98/70 mm of mercury; respirations 16 per min and temperature 37°C (98.6°F) orally. Diffuse, mild abdominal tenderness was noted on deep palpation with no rebound tenderness. Bowel sounds were hypoactive. A persistent extensive perianal rash with 3 cm area of ulceration was noted.

Initial laboratory studies showed a hemoglobin of 6.9 grams; hematocrit 19.5 percent; reticulocyte count 9 percent; leukocyte count 7,390 per cu mm, with a differential of 62 segmented neutrophils, 7 bands, 19 lymphocytes, 10 monocytes, 2 undifferentiated cells, 15 normoblasts and no eosinophils; platelet count 35,000 per cu mm. Results of a stool guaiac test were positive. Prothrombin activity was 88 percent; partial thromboplastin time 26.8 seconds; total protein 4.3 grams per 100 ml and albumin 1.9 grams per 100 ml. An x-ray film of the chest taken on admission showed old apical scarring and atelectasis in the right middle lobe. Dilated loops of small bowel with notably thickened edematous walls consistent with a paralytic ileus were seen on an x-ray of the abdomen (Figure 1). Blood, urine and sputum cultures were negative.

Supportive therapy was begun including nasogastric suction and blood transfusions. Three days after admission acute dyspnea developed with a respiratory rate of 40 to 60 per minute. The appearance of diffuse symmetrical alveolar infiltrates was noted on an x-ray film of the chest (Figure 2). Arterial partial pressure of oxygen (pO_2) was 28 mm of mercury, the partial pressure of carbon dioxide (pCO_2) 30 mm of mercury and the pH 7.49. Progressive respiratory distress with hemoptysis developed and intubation was re-

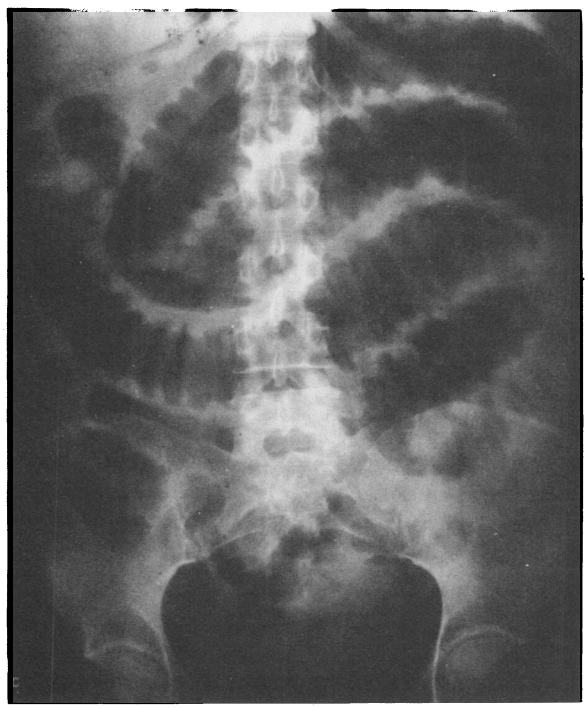

Figure 1.—Roentgenogram of the abdomen showing dilated loops of small bowel and the thickened, edematous intestinal wall.

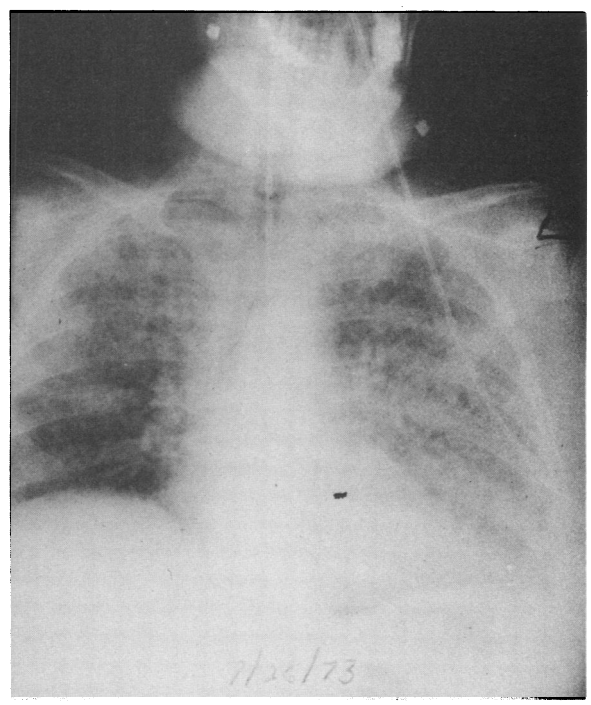

Figure 2.—Roentgenogram of the chest showing a diffuse symmetrical alveolar infiltrate.

quired. A tracheal aspirate failed to show Pneumocystis carinii, but filariform larvae of Strongyloides stercoralis were observed. Before specific therapy could be begun, a cardiorespiratory arrest occurred and the patient could not be resuscitated. Antemortem blood cultures were positive for Escherichia coli.

Postmortem Findings

Gross portmortem examination showed extensive bilateral pulmonary hemorrhage. The duodenum and proximal jejunum were distended and edematous. Most serosal and mucosal surfaces had petechiae and ecchymoses. The perineal and perianal skin was erythematous and abraded. There were several firm, irregular, marginated, maculopapular skin lesions several centimeters in diameter on the shoulders and thighs.

Microscopic examination of the skin lesions showed that the hypodermal adipose tissue contained many diffusely scattered filariform larvae of Strongyloides stercoralis. Sections of normal appearing skin failed to disclose larval forms. Histology of the lungs revealed alveolar hemorrhage with large numbers of larvae in the alveoli, septa, pleurae and blood vessels. Many larvae were present throughout the walls of the tracheobronchial tree, increasing in number toward the upper respiratory tract. Neither adult worms nor eggs were found in the respiratory tract. The heart, which grossly had small subendothelial hemorrhages, contained larvae in the chordae tendineae and within the endocardium of the atria and left ventricle. The jejunum, duodenum and ileum contained great numbers of rhabditiform and filariform larvae within all layers of their walls (Figure 3). Adult females and eggs, however, were generally confined to the mucosal and submucosal layers of the duodenum and jejunum. Diffuse colonic and prominent rectosigmoid mucosal petechiae were observed, with larval penetration of the colonic wall at various levels. An adult female was identified in only one extraintestinal location, the capsule of the pancreas. No adult males were identified. No parasites were seen in the spleen, reproductive organs or central nervous system. Many of the intrathoracic and mesenteric lymph nodes contained larvae. Larvae with bacteria in close association with the nematode cuticle were seen in various sites throughout the body. The wall of the inferior vena cava was thickened and hemorrhagic containing great numbers of larvae in a striking association with bacteria. Postmortem blood cultures were positive for Escherichia coli, Streptococcus faecalis and Enterobacter species.

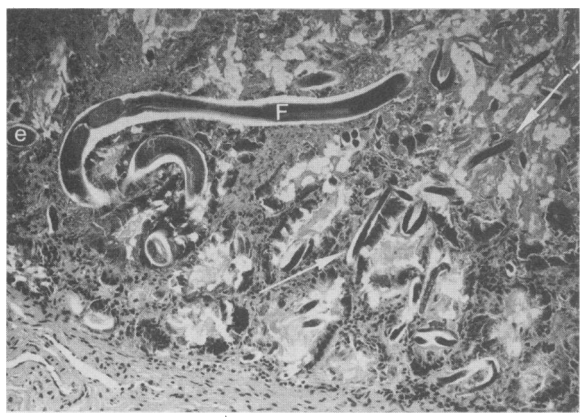

Figure 3.—Histopathologic section of the jejunum illustrating the large number of parasites. Note a gravid adult female (F), eggs (e) and larvae (arrows) of Strongyloides stercoralis (Hematoxylin and eosin; reduced from ×140).

All lymphoid tissues showed pronounced lymphocyte depletion and in general, there was little or no inflammatory response to the parasites. The bone marrow was mildly hypoplastic with a relative predominance of the eosinophilic myeloid series. No bone marrow changes or infiltrates of body tissues consistent with leukemic relapse were found.

Discussion

The intestinal threadworm Strongyloides stercoralis is endemic in tropical and subtropical areas. In the United States this infection is usually seen in immigrants and travelers; however, small endemic foci do exist—primarily in some southern states and certain institutional settings.[4,13-15] The unique life cycle of this nematode explains the necessity of detecting asymptomatic infection in the immunosuppressed patient. Ordinarily Strongyloides infection in man has a low order of pathogenicity and is usually acquired by penetration of the skin by filariform larvae. The larvae enter the blood stream, migrate through the lungs, up the bronchi into the trachea and are swallowed to eventually reach the small intestine where they mature into adult forms. Eggs deposited in the submucosa of the small bowel hatch in the tissue into rhabditiform larvae which then enter the gut lumen and are passed in the stool. Infective filariform larvae develop in the soil from the rhabditiform larvae. In contrast to other nematodes, this

parasite is capable of autoinfection and can directly reinfect its host enabling it to persist for long periods.[1,14] It is not unusual for Strongyloides to be present within a host for many years, and it has been reported to persist for as long as 51 years.[6] Our patient lived continuously in nonendemic areas for 17 years; the case serves to emphasize the occult and persistent nature of this infection, even after the patient has left an area of endemicity.

The precise mechanisms involved in autoinfection are not well understood, but under ill-defined circumstances the rhabditiform stage undergoes transformation into infective filariform larvae within the gut before leaving the host. This allows reinfection of the host at a lower level of bowel or through the perianal skin contaminated by feces. The autoinfection phenomenon appears to be accelerated into a hyperinfective stage with depression of host immune defense mechanisms.[2-12,16] As in our case, the result was a rapid and overwhelming increase in the number of infective larvae and a fulminant, usually fatal form of strongyloidiasis. The recurring perineal ulcerative skin lesions seen in our patient were possibly due to skin maceration and scratching in response to the pruritis associated with larval penetration and continuing autoinfection. The significance of the skin lesions observed at postmortem on the thighs and shoulders of this patient was not appreciated clinically. Strongyloides stercoralis is a rare cause of cutaneous larva migrans, the skin lesions being mainly confined to the perianal and adjacent areas.[17] A search for serpiginous urticarial lesions over the thighs, buttocks and abdomen may assist clinicians in the early recognition of strongyloidiasis.

Strongyloides infection in the normal host can be asymptomatic and when symptoms are present, they are usually mild and may include epigastric pain, nausea, weight loss, diarrhea and vomiting.[13,18] Rarely, fatal or severe cases of strongyloidiasis can occur with exaggerated gastrointestinal symptoms, malabsorption, dehydration, paralytic ileus or peritonitis.[5,19-24] The severity of symptoms may possibly be related to the worm burden.[3] Since the symptoms of strongyloidiasis are relatively nonspecific, a high index of suspicion in addition to a suggestive geographical history, should be all that is necessary to consider this diagnosis. Detailed questioning of our patient produced no information that would have aroused suspicion of a chronic parasitic infection and three stool specimens failed to show any ova or parasites during the initial evaluation of the patient. Early dissemination may have occurred during initial chemotherapy at about the time of the brief eosinophilia. The use of corticosteroids in this patient may have suppressed the peripheral eosinophilia that is frequently seen in the immunologically intact host during worm migration, particularly where migration through the lung is occurring.[13] Lack of an eosinophil response in severe Strongyloides infection is thought to be associated with an impairment in the immune response and a poor prognosis.[12] The generalized lymphocyte depletion and lack of an inflammatory response to the parasite seen in our patient may reflect the depressed cell mediated immunity observed in other reported cases of fatal strongyloidiasis.[12]

The roentgenographic findings of dilated small intestine with notably thickened mucosal folds are consistent with strongyloidiasis[25] (Figure 1). These findings are presumably due to diffuse worm infection, lymphatic obstruction and allergic edema in the small bowel.[19,21] On roentgenograms of the chest, patchy bronchopneumonia can be seen when migration of the larvae through the lungs takes place. In heavy dissemination through the lungs, as seen in our patient, extensive pulmonary hemorrhage and bronchopneumonia can occur and are frequent causes of death.[1,4,6,7,10,13,20] The migrating larvae may produce tissue destruction and hemorrhage in the lung by their lytic action, as well as the mechanical and allergic irritation.[26]

Migrating larvae have also been implicated in the transport of bacteria from the gut into the circulation. This has been postulated as one of the mechanisms for the sepsis and meningitis due to enteric organisms which is not infrequently observed in fatal cases.[1,5,20,21,24] The response of the fever and clinical symptoms to conventional antibiotic therapy during the second and third admissions of our patient suggests this phenomenon may have been occurring with early parasite dissemination. The observed microscopic association of bacteria with larvae is consistent with this possibility and may explain the recurrent sepsis despite the presence of a normal leukocyte count and regenerating bone marrow. As is often the case, the Strongyloides infection in our patient only became apparent terminally when larvae were recovered from a tracheal aspirate. Parasites can occasionally be recovered from sputum,[5,10,27,28]

but this appears to be the first report of larvae being recovered by tracheal aspiration.

The diagnosis of Strongyloides infection is established by microscopic examination of feces or a duodenal aspirate and showing the strongylid larvae. The ova of Strongyloides are rarely detected in stools. Tests of stools can give negative results in more than 70 percent of cases despite careful examination of both routine and concentrated stool smears.[18] Negative findings on stool examination, such as obtained in our patient before chemotherapy was begun, is not unusual in persons in whom fatal strongyloidiasis develops later.[3,5] After immunosuppression it may be several weeks before larvae appear in stool.[5] A simple test-tube cultivation procedure may be a more efficient method of detection.[29] However, by duodenal aspiration the yield of recovery can approach 90 percent.[18] A recently described method using nylon yarn attached to a weighted gelatin capsule which is swallowed and allowed to pass into the duodenum may prove useful in the recovery of Strongyloides larvae from the small bowel.[30] The string is retrieved after several hours and the adherent bile stained mucus is examined for parasites. Therefore, if other methods have failed, examination of duodenal contents may be advisable before beginning immunosuppressive therapy in patients who are from known endemic areas. As with most infections due to helminths, the use of serologic and intradermal tests are not specific enough for use as diagnostic procedures.

Thiabendazole, in a dose of 25 mg per kg of body weight twice daily for two days, is highly effective in the treatment of Strongyloides infection in the nonimmunosuppressed host and has relatively few significant untoward effects.[31] The results using this drug in the immunosuppressed host, however, have been rather poor.[3,9,10,27,32] Thus disseminated strongyloidiasis is a potentially preventable opportunistic infection if the worm is erradicated before immunosuppressive therapy is begun. It might be reasonable, therefore, to administer a course of thiabendazole to patients who are highly suspect of harboring this parasite.

Summary

A hyperinfection syndrome due to Strongyloides stercoralis led to the death of a young woman during drug-induced remission from acute lymphoblastic leukemia. Before beginning chemotherapy there was no evidence of Strongyloides infection and the patient had not been in an area endemic for strongyloidiasis for 17 years. Larvae were recovered from a tracheal aspiration done during a catastrophic pulmonary event that led to the patient's death. On necropsy, fulminant and widespread dissemination of this nematode to virtually all organ systems was seen. The case is presented to emphasize the importance of considering this infection in the immunosuppressed host in the appropriate clinical setting.

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